PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 June 1999 (01.06.99)	
International application No. PCT/GB98/02899	**Applicant's or agent's file reference** AFB/P7388WO
International filing date (day/month/year) 25 September 1998 (25.09.98)	**Priority date** (day/month/year) 26 September 1997 (26.09.97)
Applicant SACHETTO, Jean-Pierre et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:
   22 April 1999 (22.04.99)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Lazar Joseph Panakal

Telephone No.: (41-22) 338.83.38

2646210

M.H

09/508661

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
AFB/P7388WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/02899	25/09/1998	26/09/1997
International Patent Classification (IPC) or national classification and IPC		
A61K31/715		
Applicant		
MEDEVA EUROPE LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/04/1999	28.08.00
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	SANTOS, M Telephone No. +49 89 2399 8653

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/02899

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1,2,6-9,11-20	as originally filed			
3-5,5a-5b,10	as received on	21/08/1999	with letter of	16/08/1999

Claims, No.:

1-23	as received on	21/08/1999	with letter of	16/08/1999

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 23.

because:

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-23
	No:	Claims	1-2
Inventive step (IS)	Yes:	Claims	4, 17-23
	No:	Claims	1-3, 5-16
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	23 (see separate sheet)

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. The documents cited in the International Search Report (ISR) are consecutively numbered D1-D10 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in the said ISR.

2. The subject-matter of claims 1 and 2 is not considered to be new having regard to the teachings of D1 (see claim 1 and 5). Article 33(2) PCT

   Document D1 discloses an oral pharmaceutical composition containing xanthan gum as active agent for the treatment of irritable bowel syndrome, including diarrhea, constipation and pain aspects thereof.
   It is noted that, according to D1, it is the xanthan gum (in combination with an anion-binding polymer) which provides for the therapeutical effect. Whether the therapeutical effect disclosed in D1 is due to the hydrophilic activity of xanthan gum or not is not relevant for the assessment of novelty on the present composition, because D1 does already disclose oral pharmaceutical compositions comprising xanthan gum as active agent, which is the subject-matter of the above mentioned claims.
   The feature "post-gastrically available delayed release" in claim 1 is not considered to be clear (Article 6 PCT). Therefore, this feature has been ignored for the assessment of the novelty of claim 1.

3. Documents D3, D4-D10 disclose compositions comprising xanthan gum or HPMC as excipient and not as therapeutic active agent.

   Thus, the subject-matter of claims 1-23 is considered to be new over the teachings of D3, D4-D10.

4. The subject-matter of claims 1-3 and 5-16 does not appear to involve an inventive step. Article 33(3) PCT
   Document D1 is considered to be the closest prior art.
   This document teaches compositions comprising a polysaccharide as the active agent and being useful in medicine.

The provision of a rectally administrable composition (see present claims 7-15) instead of an oral composition of the active compound according to the invention is considered to be obvious for the skilled person. The same comments apply for the provision of a "delayed" release composition (claim 6).

5. The subject-matter of claims 4 and 17-23 is considered to be new and to involve an inventive step. Articles 33(2) and (3) PCT

None of the documents cited in the International search report discloses a composition containing xanthan gum or HPMC as the sole therapeutically active ingredient (present claim 4) or the use of xanthan gum or HPMC as therapeutically active agents in the manufacture of a medicament for the treatment of IBD (claims 17-22) or a method for the treatment of IBD by administering xanthan gum or HPMC.

6. Claim 1 is not clear (Article 6 PCT), because the expression "post-gastrically available delayed release" is not considered to be clear.

7. In view of the unavailability of the present priority document it has not been possible for the IPEA to establish if the present claims are entitled to their earliest declared priority date. The present assessment of novelty and inventive step has been made on the assumption that the claims are entitled to their earliest declared priority date.
The following document D2, however appears to disclose the subject-matter of claims 1, 3-5, 7, 8, 11, 12, 14-22 and may, therefore, be considered to be a relevant earlier application by certain authorities (see states designated in respect of this earlier application). Thus, it may be helpful to note that this document is potentially relevant to lack of novelty of the above mentioned claims.

8. For the assessment of the present claim 23 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can

also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

9. The document WO-A-9401436 cited on page 4, line 20 should read: WO-A-9404136.

10. The amendments filed with the letter dated 16.08.99 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.
The amendments concerned are the following:

-the deletion of "substantially" on page 10, line 36.

Article 34

Numerous compounds have been examined in the last twenty years to find effective measures for the treatment of IBD. Such compounds include azathioprine, arsenicals, disodium cromoglycate, metronidazole, lignocaine, 5-aminosalicyclic acid (5-ASA), fish oils, thalidomide and cyclosporin. The wide diversity of treatments, is an indication of the complexity and intransigence of IBD.

GB-A-1538123 (published 8th January 1979) disclosed the treatment of diverticulitis with a fibrous cellulosic material and a carboxylic polymer or salt which absorbs water and swells above pH 4. Specified carboxylic polymers include sodium carboxymethylcellulose (sodium CMC).

EP-A-0351987 (published 24th January 1990) disclosed the use of a polyacrylate, preferably a carbomer, for the treatment of IBD by oral or rectal administration.

US-A-4917890 (published 17th April 1990) disclosed the treatment of ulcerative colitis with a mucilaginous polysaccharide aloe extract.

WO-A-9101129 (published 7th February 1991 discloses enemas formed by the addition of water to a dry composition containing an active and excipients. Exemplified actives include 5-aminosalicylic acid and other drugs for the treatment of IBD (including proctitis). Preferably, the excipients comprise a hydrophilic gelling agent, a foam inhibitor and, optionally, wetting agents, flow improvers, buffers and water-soluble polymers. The exemplified gelling agents include HPMC.

WO-A-9216214 (published 1st October 1992) discloses the treatment of IBD-diarrheal phase/type by topical delivery of 5-aminosalicylic acid to the intestinal tract. Reference is made to both oral and rectal administration and there is specific reference to DRO dosage form. HPMC and xanthan gum are amongst preferred viscosity agents which may be present in the formulation. The tablets of Example VII contain 5-

ASA granules coated with HPMC; the coated tablets of Examples VIII to XI contain HPMC as an excipient; and the enemas of Examples XIV to XVI contain xanthan gum as an excipient. There is no suggestion that HPMC or xanthan gum are themselves active in the treatment of IBD.

EP-A-0517274 (published 9th December 1992) discloses enemas containing 5-aminosalicylic acid and titanium dioxide. Optional components include viscosity-enhancing substances of which the only exemplification is xanthan gum.

FR-A-2692484 (published 24th December 1993) discloses enterically coated tablets containing 4-aminosalicylic acid in a hydrophilic matrix. Exemplified materials of the hydrophilic matrix include HPMC and specific reference is made to use of the tablets in treating haemorrhage rectocolitis and Crohn's disease. There is no reference to any pharmacological activity for HPMC.

WO-A-9401436 (published 3rd March 1994; corresponding to US-A-5380522) disclosed treatment of irritable bowel syndrome (IBS) with an oral medicament of an anion-binding polymer and a hydrophilic polymer. Although the anion-binding polymer and hydrophilic polymer can be administered separately, it is stated that only the combination of anion-binding polymer and hydrophilic polymer is effective in preventing and relieving symptoms IBS. The anion-binding polymer is present as a bile acid sequestrant but there is no indication in the reference that, as a class, the hydrophilic polymer has any function other than its hydrophilic activity. Specifiedhydrophilic polymers include xanthan gum but there is exemplification of its use; no suggestion that it has any pharmacological effect in IBS, and no mention of coating or otherwise providing a delayed release oral (DRO) formulation.

WO-A-9407540 (published 14th April 1994; corresponding to EP-A-0620012 & US-A-5518711) disclosed an X-ray contrast

medium containing 15-35 w/v% $BaSO_4$ and 0.15-0.6 w/v% xanthan gum dispersed in water. Lower xanthan gum concentrations are used with higher $BaSO_4$ concentrations. The medium is useful for double contrast enema examination of the large and the small intestine to detect *inter alia* Crohn's disease.

Sandborn et al (Gastroenterology 1994, 106, 1429-1435) reported a placebo-controlled trial of cyclosporin enemas in the treatment of mildly to moderately active left-sided ulcerative colitis. The vehicle for both the test and placebo enemas comprised 60 cm^3 water, 5 mg sorbitol (to make the vehicle isomolar) and 500 mg carboxymethylcellulose (CMC) (to suspend the hydrophobic cyclosporin). The placebo enema contained 3.5 cm^3 olive oil and use of this enema resulted in clinical improvement in nine out of twenty patients tested.

WO-A-9603115 (published 8th February 1996) disclosed aqueous foamable compositions having a delayed foaming action on expulsion from a pressurised container, comprising a water-immiscible liquefied gas, a water soluble polymer, and optionally, *inter alia* , a muco-adhesive agent. Exemplified water-soluble polymers include xanthan gum and HPMC and exemplified muco-adhesive agents include CMC. The compositions are of particular use for rectal or vaginal administration of pharmaceuticals to treat *inter alia* ulcerative colitis or Crohn's disease.

JP-A-08198757 (published 6th August 1996) discloses the use of high amylose starch, preferably administered with food materials, for the treatment of chronic ulcerative colitis.

WO-A-9630021 (published 3rd October 1996) discloses the treatment of IBD by topical administration to the colon of azathioprine. Reference is made to both oral and rectal administration and the oral dosage form can be enterically coated to delay release to the terminal ileum and/or colon.

There is a general reference to the use of gums and modified celluloses as carriers in enema formulations (see page 4, lines 1/3). The foam enemas of Examples 1 and 2 contain xanthan gum as suspending agent.

WO-A-9640078 (published 19th December 1996) discloses the use of certain hydrocolloids to provide delayed release for drugs in the treatment of IBS and IBD. The delayed release is provided by degrading of the hydrocolloid by enzymes present in the lower intestinal tract. Reference is made to the use of HPMC as an excipient and the tablets of Examples 1 and 4 contain HPMC.

Ciftci et al (Int. J. Pharm., 145 (1996) 157-164) discloses the use of a rat model to demonstrate that an enteric-coated HPMC granular formulation is capable of targeting or persisting in the colonic region. It is proposed that this system should be used to provide a drug delivery system selectively targeting the colorectal region. There is no reference to the treatment of IBS or IBD or any suggestion that HPMC has any pharmacological effect.

The present Inventors found that xanthan gum and HPMC are effective *per se* for the treatment of IBD. This is surprising because, as indicated above, these materials are widely used in pharmaceutical compositions because of their assumed lack of pharmacological activity.

WO 98/01112 (published 15th January 1998; after the claimed priority dates of the present Application) discloses the treatment of distal IBD with a hydrogel formulation consisting essentially of a gelling agent and water with the optional presence of a pH-adjusting agent, plasticizer and/or surfactant. The preferred gelling agents include HPMC and sodium CMC. The only specified distal IBD is ulcerative colitis.

According to a first aspect of the present invention, there is provided the use of a polysaccharide selected from

xanthan gum and HPMC as a therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative proctosigmoiditis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, pouchitis, radiation colitis, and antibiotic-associated colitis. Xanthane gum and HPMC have been found to be particularly useful in the treatment of IBD conditions (such as pouchitis and left-sided ulcerative colitis) normally refractive to conventional therapy.

In a second aspect, the present invention provides a rectally administrable or post-gastrically available delayed release oral (DRO) pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in an amount effective to treat IBD, together with a pharmaceutically acceptable carrier or vehicle. DRO compositions pass through the stomach substantially unaltered and deliver their active ingredient (which is within the tablet, capsule etc.) typically to the ileum up to and including the colon (i.e. where the diseased mucosa is).

According to a third aspect, the present invention provides a rectally administrable or post-gastrically available DRO pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising a polysaccharide selected from xanthan gum and HPMC as the

ileum and/or in the colon of the patient. Enteric coatings remain intact in the stomach, but dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution for the coating used.

A DRO formulation can also be achieved by coating a powder or microgranular formulation of the polysaccharide with coatings as mentioned above. The coated microgranules or material may then be compressed into tablets or packed into hard gelatin capsules suitable for oral administration. Suitable coatings and thicknesses to achieve this sustained release are disclosed in EP-A-0572486 (incorporated herein by reference).

The DRO form may optionally also be formulated to give a sustained release of the polysaccharide. The delayed release can be obtained, for example, by complexing the polysaccharide with a polyacrylic acid derivative (a polysaccharide polyacrylate complex) more particularly a polysaccharide carbomer complex. Alternatively particles of the polysaccharide complex could be incorporated into a hydrophobic matrix such as Gelucire™ (Gattefosse, France).

Aqueous film-coating technology is advantageously employed for the enteric coating of pharmaceutical dosage forms. A useful enteric coating is one that remains intact in the low pH of the stomach, but readily dissolves when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5, preferably pH 5 to 7, most preferably pH 5.5 to 6.8, depending on the chemical composition of the enteric coating. The thickness of the coating will depend on the solubility characteristics of the coating material and the site to be treated.

By "delayed release" we mean that release is post-gastrically and by "sustained release" we mean that the total release of the polysaccharide is slow

CLAIMS

1. A rectally administrable or post-gastrically available delayed release oral (DRO) pharmaceutical composition for the treatment or prophylaxis of inflammatory bowel disease (IBD), said composition comprising a polysaccharide selected from xanthan gum and hydroxypropylmethylcellulose (HPMC) as a therapeutically active agent in an amount effective to treat inflammatory bowel disease, together with a pharmaceutically acceptable carrier or vehicle.

2. A composition as claimed in Claim 1, wherein the polysaccharide is xanthan gum.

3. A composition as claimed in Claim 1, wherein the polysaccharide is HPMC

4. A composition as claimed in any one of the preceding claims, wherein the polysaccharide is present as the sole therapeutically active ingredient.

5. A composition as claimed in any one of the preceding claims which is a DRO composition.

6. A composition as claimed in Claim 5 which DRO composition is an enteric coated dosage form adapted to release its contents within the region of the jejunum to the colon.

7. A rectally administrable composition as claimed in any one of Claims 1 to 4.

8. A rectally administrable composition as claimed in Claim 7 which is a liquid enema or foam enema.

9. A liquid enema as claimed in Claim 8, wherein the polysaccharide is xanthan gum in a concentration of 0.4 to 2 % w/w (based on the composition).

10. A foam enema as claimed in Claim 8, wherein the polysaccharide is xanthan gum in a concentration of 1.4 to 2.5 w/w (based on the composition).

11. A liquid enema as claimed in Claim 8, wherein the polysaccharide is HPMC in a concentration of 1 to 20 % w/w (based on the composition).

12. A liquid enema as claimed in Claim 9, wherein the polysaccharide is HPMC in a concentration of 5 to 20 % w/w (based on the composition). p. 9 l 14

13. A foam enema as claimed in Claim 8, wherein the polysaccharide is HPMC in a concentration of 2.5 to 25 % w/w (based on the composition).

14. A rectally administrable composition as claimed in Claim 7 or Claim 8, wherein the polysaccharide is xanthan gum in an amount of 400 to 2000 mg per unit dose.

15. A rectally administrable composition as claimed in Claim 7 or Claim 8, wherein the polysaccharide is HPMC in an amount of 1 to 20 g per unit dose..

16. A DRO composition as claimed in Claim 5 or Claim 6 in unit dose containing 400 to 2,000 mg of the polysaccharide per unit dose. p. 11 l 21,2

17. The use of a polysaccharide selected from xanthan gum and hydroxypropylmethylcellulose (HPMC) as a therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of inflammatory bowel disease (IBD).

18. A use as claimed in Claim 17, wherein the polysaccharide is the sole therapeutically active agent in the medicament.

19. A use as claimed in Claim 17 or Claim 18 wherein the disease state is pouchitis.

20. A use as claimed in Claim 17 or Claim 18 wherein the disease state is left-sided ulcerative colitis.

21. A use as claimed in Claim 17 or Claim 18 wherein the disease state is Crohn's Disease.

22. A use as claimed in any one of Claims 17 to 21, wherein the medicament is a composition as defined in any one of Claims 1 to 16.

23. A method for the treatment or prophylaxis of inflammatory bowel disease (IBD) comprising contacting the diseased mucosa of the gastro-intestinal tract with a therapeutic amount of a polysaccharide selected from xanthan gum and hydroxypropylmethylcellulose (HPMC).

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/715, 9/10

A1

(11) International Publication Number: **WO 99/16454**

(43) International Publication Date: 8 April 1999 (08.04.99)

(21) International Application Number: PCT/GB98/02899

(22) International Filing Date: 25 September 1998 (25.09.98)

(30) Priority Data:

9720590.0	26 September 1997 (26.09.97)	GB
9725346.2	28 November 1997 (28.11.97)	GB

(71) Applicant *(for all designated States except US)*: MEDEVA EUROPE LIMITED [GB/GB]; 10 St. Jame's Street, London SW1A 1EF (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SACHETTO, Jean-Pierre [FR/CH]; Duchelweiher 13, CH-4051 Basel (CH). SANDBORN, William, Jeffery [US/US]; 1132-7th Street, S.W., Rochester, MN 55902 (US). TREMAINE, William, John [US/US]; 625 Memorial Parkway, S.W., Rochester, MN 55905 (US).

(74) Agent: BURFORD, Anthony, F.; W.H. Beck, Greener & Co., 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

(57) Abstract

A polysaccharide selected from xanthan gum and HPMC is used for the treatment or prophylaxis of IBD, especially Crohn's Disease, left-sided ulcerative colitis or pouchitis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

This invention relates to use of xanthan gum or hydroxypropylmethylcellulose (HPMC), particularly in the form of enemas for the treatment of inflammatory bowel disease (IBD), and to orally administrable and rectally/vaginally administrable compositions containing xanthan gum or HPMC as a therapeutically active agent.

Xanthan gum (CAS registry no. 1138-66-2) is described in USP NF XVI (p161) as a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with Xanthomonas campestris. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and is prepared as the sodium, potassium or calcium salt. It is widely used in pharmaceutical compositions as an emulsifying, stabilising and/or thickening agent.

HPMC (CAS registry no. 9004-65-3), otherwise known as hypromellose, is used as a suspending agent, tablet excipient, demulcent and/or viscosity increasing agent in pharmaceutical compositions. It is been used as a capsule or tablet coating, but the coating is soluble in gastric juices, and so would deliver the active in the capsule in the stomach.

IBD covers chronic non-specific inflammatory conditions of the gastro-intestinal tract, of which the two major forms are Crohn's disease and ulcerative colitis. The aetiology of these diseases is uncertain. Many inflammatory mediators have been proposed including prostanoids, leukotrienes, platelet activating factor, cytokines, and free oxygen radicals. Although specific inhibitors of most of these have been tried in experimental models, the most effective drugs currently available for these diseases have a broad activity against inflammatory processes.

Crohn's disease is characterised by thickened areas of the gastro-intestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas. Affected areas may occur in any part of the gastro-intestinal tract, although the terminal ileum is frequently involved, and they may be interspersed with areas of relatively normal tissue. Fistulas and abscesses may develop. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss and rectal bleeding.

In ulcerative colitis, disease is continued to the colon and rectum. Inflammation is superficial but continuous over the affected area and granulomas are rare. In mild disease, the rectum alone may be affected (proctitis). In severe disease ulceration is extensive and much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication.

Abdominal colectomy with mucosal proctectomy and ileal pouch-anal anastomosis is the preferred treatment for most patients with ulcerative colitis who require surgery. Pouchitis, the most common long-term complication of the procedure, occurs in up to 49% of patients at 10 years. Chronic pouchitis is distinguished from acute pouchitis by duration of symptoms for more than 4 weeks. The aetiology of pouchitis is unknown but it appears that both a history of ulcerative colitis and increased bacterial concentrations (relative to the normal ileum) are factors.

Currently, there is no satisfactory treatment for patients with chronic pouchitis who fail to respond to empiric antibiotic therapy. Although metronidazole is effective in some patients, long-term use is limited by concerns for neurotoxicity with peripheral neuropathy.

Numerous compounds have been examined in the last twenty years to find effective measures for the treatment of IBD. Such compounds include azathioprine, arsenicals, disodium cromoglycate, metronidazole, lignocaine, 5-aminosalicyclic acid (5-ASA), fish oils, thalidomide and cyclosporin. The wide diversity of treatments, is an indication of the complexity and intransigence of IBD.

GB-A-1538123 (published 8th January 1979) disclosed the treatment of diverticulitis with a fibrous cellulosic material and a carboxylic polymer or salt which absorbs water and swells above pH 4. Specified carboxylic polymers include sodium carboxymethylcellulose (sodium CMC).

EP-A-0351987 (published 24th January 1990) disclosed the use of a polyacrylate, preferably a carbomer, for the treatment of IBD by oral or rectal administration.

US-A-4917890 (published 17th April 1990) disclosed the treatment of ulcerative colitis with a mucilaginous polysaccharide aloe extract.

WO-A-94/01436 (published 3rd March 1994; corresponding to US-A-5380522) disclosed treatment of irritable bowel syndrome (IBS) with an oral medicament of an anion-binding polymer and a hydrophilic polymer. Exemplified anion-binding polymers include xanthan gum.

WO-A-9407540 (published 14th April 1994; corresponding to EP-A-0620012 & US-A-5518711) disclosed an X-ray contrast medium containing 15-35 w/v% $BaSO_4$ and 0.15-0.6 w/v% xanthan gum dispersed in water. Lower xanthan gum concentrations are used with higher $BaSO_4$ concentrations. The medium is useful for double contrast enema examination of the large and the small intestine to detect *inter alia* Crohn's disease.

Sandborn et al (Gastroenterology 1994, 106, 1429-1435) reported a placebo-controlled trial of cyclosporin enemas in the treatment of mildly to moderately active left-sided ulcerative colitis. The vehicle for both the test and placebo enemas comprised 60 cm^3 water, 5 mg sorbitol (to make the vehicle isomolar) and 500 mg carboxymethylcellulose (CMC) (to suspend the hydrophobic cyclosporin). The placebo enema contained 3.5 cm^3 olive oil and use of this enema resulted in clinical improvement in nine out of twenty patients tested.

WO-A-9603115 (published 8th February 1996) disclosed aqueous foamable compositions having a delayed foaming action on expulsion from a pressurised container, comprising a water-immiscible liquefied gas, a water soluble polymer, and optionally, *inter alia* , a muco-adhesive agent. Exemplified water-soluble polymers include xanthan gum and HPMC and exemplified muco-adhesive agents include CMC. The compositions are of particular use for rectal or vaginal administration of pharmaceuticals to treat *inter alia* ulcerative colitis or Crohn's disease.

JP-A-08198757 (published 6th August 1996) discloses the use of high amylose starch, preferably administered with food materials, for the treatment of chronic ulcerative colitis.

The present Inventors found that xanthan gum and HPMC are effective *per se* for the treatment of IBD. This is surprising because, as indicated above, these materials are widely used in pharmaceutical compositions because of their assumed lack of pharmacological activity.

WO 98/01112 (published 15th January 1998; after the claimed priority dates of the present Application) discloses the treatment of distal IBD with a hydrogel formulation consisting essentially of a gelling agent and water with the optional presence of a pH-adjusting agent, plasticizer

and/or surfactant. The preferred gelling agents include HPMC and sodium CMC. The only specified distal IBD is ulcerative colitis.

According to a first aspect of the present invention, there is provided the use of a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative proctosigmoiditis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, pouchitis, radiation colitis, and antibiotic-associated colitis. Xanthane gum and HPMC have been found to be particularly useful in the treatment of IBD conditions (such as pouchitis and left-sided ulcerative colitis) normally refractive to conventional therapy.

In a second aspect, the present invention provides a post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in an amount effective to treat IBD, together with a pharmaceutically acceptable carrier or vehicle. DRO compositions pass through the stomach substantially unaltered and deliver their active ingredient (which is within the tablet, capsule etc.) typically to the ileum up to and including the colon (i.e. where the diseased mucosa is).

According to a third aspect, the present invention provides a post-gastrically available DRO or rectally administrable pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising a polysaccharide selected from xanthan gum and HPMC as the

sole therapeutically active agent together with a pharmaceutically acceptable carrier or vehicle.

In a fourth aspect, the present invention provides the use of a polysaccharide selected from xanthan gum and HPMC as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

In yet another aspect of the present invention, there is provided a method for the treatment or prophylaxis of IBD comprising contacting the diseased mucosa of the gastro-intestinal tract with a therapeutic amount of a polysaccharide selected from xanthan gum and HPMC.

The polysaccharide can be used in the form of pharmaceutically acceptable salts of such as with alkali metals, usually sodium or potassium and alkaline earth metals, usually calcium or barium.

When the polysaccharide is present as the sole active agent, then no other therapeutically active agent such as 5-ASA or a corticosteriod will be present. Optionally, however, other therapeutic agents currently used or proposed for treating IBD can also be used sequentially in a different dosage form or concomitantly in the same dosage form as the polysaccharide. Examples of other such therapeutic agents are 5-ASA; immune modifiers such as azathioprine, cyclosporin and FK506; corticosteroids such as prednisolone, budesonide and hydrocortisone; antibiotics such as metronidazole, ciprofloxacin, amoxicillin, tetracycline and sulphamethoxazole; antidiarreals such as loperamide and codeine sulphate; and local anaesthetics such as lignocaine.

The polysaccharide may be incorporated into a pharmaceutical composition to be administered either rectally, e.g. as an enema, or orally, for example, in coated tablets or capsules as described below. Also, the

polysaccharide may be formed into microgranules and coated, for example with Eudragit™ L or S and contained within a capsule similarly coated. In all solid compositions, it is preferable to include a disintegrant. Still further, the polysaccharide may be formulated in a number of dosage forms, e.g. uncoated or coated solid dosage forms for delayed release oral administration, for example using polymers in the Eudragit™ product range.

According to a preferred embodiment of the present invention, the pharmaceutical composition takes the form of an enema formulation such as a liquid or foam enema which is rectally administered to the lower colon. The enema formulations suitably comprise the polysaccharide dissolved or dispersed in a suitable flowable carrier vehicle, such as deionised and/or distilled water. The formulation can be thickened with one or more thickeners, can contain a buffer, and can also comprise an effective amount of a lubricant such as a natural or synthetic fat or oil, e.g. a tris-fatty acid glycerate or lecithin. Non-toxic non-ionic surfactants can also be included as wetting agents and dispersants. Unit doses of enema formulations can be administered from pre-filled bags or syringes. In the case of a pressurised enema formulation the carrier vehicle may also comprise an effective amount of a foaming agent such as *n*-butane, propane or *i*-butane, or the foaming agent/propellant could be held separately from the composition such as in a bag-in-bag or bag-in-can system as described in WO-A-9603115 (incorporated herein by reference). Enema foams may also comprise expanding agents and foam-stabilisers.

The viscosity of the enema is preferably 10,000 to 70,000 mPa.s more preferably 10,000 to 70,000 mPa.s and most preferably 10,000 to 40,000 mPa.s. The pH is preferably 3.5 to 7.5, especially 6.5 to 7.5.

A suitable dosage for xanthan gum in an enema or foam enema is 200 to 2000 mg, preferably 250 to 2000 mg, more

preferably 250 to 1650 mg, more preferably still 400 to 1650 mg, especially 550 to 1000 mg, in an aqueous or non-aqueous carrier. The volume of a liquid enema is typically 50 to 200 cm^3 preferably about 100 cm^3. A suitable % w/w of xanthan gum in an enema is (based on 100 cm^3 enema) is 0.2% to 2% w/w, more preferably 0.3% to 2% w/w, more preferably still 0.4% to 2% w/w, more preferably still up to 1.65% w/w, and still more preferably 0.55% to 1%. Suitably the volume of a foam enema is 20 to 40 cm^3. Based on the above preferred dosages, a suitable % w/w of xanthan gum in a foam enema (based on 40 cm^3 foam enema) is 1% to 4.25% w/w, more preferably 1.4% to 2.5%. A buffer is preferably added to the liquid or foam enema of xanthan gum to stabilise the pH. When a buffer is used it increases the viscosity and as a result, the maximum % w/w of xanthan gum that can be incorporated in the enema is about 1.7% w/w.

Typically the viscosity grade of xanthan gum used in a rectally administrable or DRO composition of the invention is 1,200 to 1,600 cP (mPa.s) at 1%.

Typically the viscosity grade of HPMC used in a rectally administrable or DRO composition of the invention is 3 to 100,000 cP (mPa.s). More particularly the grade of HPMC varies depending on the degree of hydroxypropoxy and methoxy substitution. Thus, preferably the degree of methoxy substitution is 15 to 30%, more preferably 19 to 30% such as 19 to 24% and 27 or 28 to 30%. The degree of hydroxypropoxy substitution is preferably 2 to 15%, more preferably 4 to 12%, such as 7 to 12% or 4 to 7.5% The commercially available grades of HPMC include the following:

Product	% Methoxyl	% Hydroxypropoxyl	Viscosity cP (Mpa.s)	Relative Rate of Hydration
METHOCEL™ K Premium	19-24	7-12	3, 100, 4000, 15000, 100000	Fastest
METHOCEL™ E Premium	28-30	7-12	3, 5, 6, 15, 50, 4000	Next fastest
METHOCEL™ F Premium	27-30	4-7.5	50, 4000	Slower

The large range of viscosities allows a high dosage liquid enema or foam enema of HPMC to be formed by using a low viscosity grade of HPMC (i.e. a higher dosage than xanthan gum can be incorporated since the viscosity of the HPMC is less limiting). A suitable dosage of HPMC for a liquid enema or foam enema is 0.2 to 20 g, preferably 1 to 20g, more preferably 2 to 10 g, still more preferably 5 to 10 g for some IBD disease states and 1 to 5 g for other IBD disease states. A suitable % w/w of HPMC in a liquid enema or foam enema (based on 100 cm^3) is 0.2% to 20% w/w, preferably 1% or 2% w/w to 20%, more preferably to an upper limit of 10% w/w, more preferably still 5% to 10%. A suitable % w/w of HPMC in a foam enema (at 40 cm^3) is 1% to 50% w/w, more preferably 2.5% to 25% w/w, such as at least 7.5% w/w.

In a further embodiment of the invention, the polysaccharide is administered to the small intestine or colon of a patient by oral ingestion of a post-gastric delayed release (DRO) unit dosage form such as a tablet or capsule, comprising an effective amount of polysaccharide which is enterically coated so as to be released from the unit dosage form in the lower intestinal tract, e.g. in the

ileum and/or in the colon of the patient. Enteric coatings remain intact in the stomach, but dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution for the coating used.

A DRO formulation can also be achieved by coating a powder or microgranular formulation of the polysaccharide with coatings as mentioned above. The coated microgranules or material may then be compressed into tablets or packed into hard gelatin capsules suitable for oral administration. Suitable coatings and thicknesses to achieve this sustained release are disclosed in EP-A-0572486 (incorporated herein by reference).

The DRO form may optionally also be formulated to give a sustained release of the polysaccharide. The delayed release can be obtained, for example, by complexing the polysaccharide with a polyacrylic acid derivative (a polysaccharide polyacrylate complex) more particularly a polysaccharide carbomer complex. Alternatively particles of the polysaccharide complex could be incorporated into a hydrophobic matrix such as Gelucire™ (Gattefosse, France).

Aqueous film-coating technology is advantageously employed for the enteric coating of pharmaceutical dosage forms. A useful enteric coating is one that remains intact in the low pH of the stomach, but readily dissolves when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5, preferably pH 5 to 7, most preferably pH 5.5 to 6.8, depending on the chemical composition of the enteric coating. The thickness of the coating will depend on the solubility characteristics of the coating material and the site to be treated.

By "delayed release" we mean that release is substantially post-gastrically and by "sustained release" we mean that the total release of the polysaccharide is slow

and sustained over a period of time, as opposed to being released as a bolus.

The majority of the release will be targeted to the part of the small intestine or colon where the active disease is prevalent and this varies for Crohn's disease and ulcerative colitis. Thus typically for an enteric coated capsule, the enteric coating should dissolve in the pH of the jejunum (about pH 5.5), ileum (about pH 6) or colon (about pH 6-7) so as to release the majority of the active from the jejunum to the colon - where most of the active disease is located in IBD. More particularly in the case of Crohn's disease most of the active disease is around the terminal ileum and so the enteric coating should dissolve about pH 5.5 to 6. In the case of ulcerative colitis, the disease is mostly in the colon and therefore the enteric coating should dissolve about pH 6 to 7, more particularly about pH 6.8.

Suitably the unit dosage of the polysaccharide in the delayed release oral composition is 200 to 2000 mg, preferably 250 to 2000 mg, more preferably 250 to 1650 mg, more preferably still 400 to 1650 mg, especially 550 to 1000 mg. A suitable % w/w of the polysaccharide in a DRO of the invention is 40 to 90% w/w, more preferably 60 to 80% w/w.

The above also is approximate to the total daily dosage and can be achieved by one or more unit dosages taken once, twice, three or more times daily. For example the total daily dosage is typically 200 to 6000 mg, preferably having a upper dosage limit of about 4000 mg and a lower limit of about 400 mg.

The DRO formulation can be provided as an enteric coated capsule containing the polysaccharide and having a coating thickness and dissolution profile as described in EP-A-0097651 (the contents of which are incorporated herein by reference). Suitable coating include cellulose acetate

phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose or polyvinyl acetate phthalate but the preferred coating material is an anionic polymer, especially one having the dissolution profile specified in EP-A-0097651, optionally in admixture with a neutral insoluble but permeable polymer. The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anionic polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers such as poly(methacrylic acid, methyl methacrylate) in which the ratio of free acid groups to ester groups is about 1:1 (e.g. those available from Röhm Pharma GmbH under the Trade Mark EUDRAGIT S). A neutral polymer coating, more specifically poly(ethylacrylate-methylmethacrylate) (e.g. Eudragit™ NE30D) may also be useful in some instances.

Examples of methacrylates (in the Eudragit™ range) for use as enteric coatings in accordance with the invention are as follows.

Chemical name	Trade name	CAS number
Poly(methacrylic acid, methyl methacrylate) 1:1	Eudragit™ L 100 Eudragit™ L 12.5 Euragit™ L 12.5 P	[25806-15-1]
Poly(methacrylic acid, ethyl acrylate) 1:1	Eudragit™ L 30 D-55 Eudragit™ L 100-55	[25212-88-8]
Poly(methacrylic acid, methyl methacrylate) 1:2	Eudragit™ S 100 Eudragit™ S 12.5 Eudragit™ S 12.5 P	[25086-15-1]

In general coating thicknesses of about 25 to 200 μm, and especially 75 to 150 μm, are preferred using about 3 to 25 mg, preferably 8 to 15 mg of acidic coating material per

cm^2 of tablet or capsule surface. The precise coating thickness will however depend upon the solubility characteristics of the acidic material used and site to be treated.

In another preferred DRO or rectally administrable embodiment of the invention, sub 150μm particles of the polysaccharide or complex thereof (e.g. carbomer complex) is coated (partially or completely) or impregnated with a water insoluble anionic polymer. This prevents the formation of lumps and encourages the resulting hydrophobic particles of polysaccharide to disperse and coat the bowel wall when the contents of the DRO tablet or capsule are released. This technology is described in more detail in International Patent Application no. PCT/GB97/01847 (WO-A-9802573) (incorporated herein by reference).

By "sub 150μm particles", we mean such that 100% of particles in the DRO will pass through a 150 μm sieve. It is preferred that 100% of the hydrophillic carbomer particles pass a 100 μm sieve screen (i.e. they are sub 100 μm), more preferably at least 90%, especially at least 95%, of the hydrophilic particles pass a 63 μm sieve screen, more preferably a 50 μm sieve screen. The precise particle size must be small enough to provide a composition with a suitable degree of hydrophobicity following coating with the anionic polymer. Preferred particle size may vary according to the nature and amount of the cation present in the complex and the nature and amount of the anionic polymer.

The amount of anionic polymer used will depend upon the nature and amount of the cation present in the salt, the nature of the impregnating anionic polymer, and the degree of hydrophobicity required. A suitable amount can be determined by simple experimentation but usually the anionic polymer will be present in an amount of 10 to 50%, preferably 20 to 40, more preferably 25 to 35 and especially about one third, based on the weight of the carbomer

complex. Having regard to the small particle size, the amount of polymer will be less than the theoretical amount required to coat the particles, and the swelling and dissolution of the carbomer will not be controlled by pH.

The polysaccharide particles are impregnated/ hydrophobised by milling and passing through a suitable sieve (as aforementioned), stirring the sieved particles into a mixture of e.g. isopropanol and water (solvent) and partly methyl esterified methacrylic acid polymer (e.g. Eudragit™ S100) at from 20 to 40% by weight of the polysaccharide particles (the solvent/coating solution having previously been agitated until clear), stirring and then evaporating the solvent under vacuum at about 50-70 °C to leave coated polysaccharide particles. Thereafter the resulting powder can be filled into gelatin capsules ready for enteric coating.

The invention will now be described by way of the following Examples.

Example 1 : Enema with HPMC.

947.6 g of purified water is preserved with 2 g of methyl and 0.4 g propyl parabens. 50 g (dry basis) of HPMC (Methocel E) low viscosity grade (50 cP/mPa.s) is dissolved under mechanical stirring at room temperature. The solution is degassed (air) under reduced pressure in an oven. A clear viscous enema is obtained having pH 6.9, viscosity (spindle 64, 1.5 rpm - 20°C on Brookfield DV 11): 4,000 mPa.s. The formation is packed in a bag-in-can canister or in an enema plastic pouch or in a PE bottle all having a 100 g enema capacity delivery, thus delivering a full dose of 5,000 mg HPMC.

Example 2 : Foam Enema Formulation with Xanthan Gum.

14,871 g of purified water containing 22 g of dissolved methyl paraben and 2 g of dissolved propyl paraben as preservatives were placed in a 20 litre Moltomat-Universal™ MMU 20 homogenizer. Then 435g of xanthan gum (Keltrol™ TF) having a water content of 7.6% were dispersed in the preserved water under efficient homogenization and reduced pressure.

30 g of unbleached lecithin were then added and dispersed under homogenization and reduced pressure. At this stage the pH of the viscous gel obtained was 6.3. A solution then made of 0.45 g sodium hydroxide pellets and 20 g of water was added and dispersed under reduced pressure. The pH then was 6.93. Finally 155 g of Polysorbate 80 (non-ionic surfactant) and 4 g of Citral (perfume) were added and dispersed under reduced pressure.

The final foam enema appeared as a slightly hazy gel, having a pH of 7.04 and a viscosity of 40,000 mPa.s at 20°C as measured using a Brookfield DV II viscometer (1.5 rpm, spindle 63).

A foam enema was then produced using this formulation by adding 2.2 g of n-butane per 100 g of the above formulation in a pressurised mixing unit and the mixture was then filled into bag-in-can aerosol canisters. Each canister contained 23 g of the mixture from which 21 g of foam was delivered through a valve and an applicator, i.e. about 530 mg of xanthan gum per delivered dose.

Example 3 : Liquid Enema Formulation with Xanthan Gum.

To 4,906 g of purified water containing 10 g of dissolved methyl paraben and 2 g of dissolved propyl paraben used as preservatives, 58.95 g of xanthan gum (Keltrol™ TF) containing 6.7% water (i.e. 55 g dry basis) was added in an

homogenizer and dispersed under efficient homogenization under reduced pressure. The pH of the gel obtained was 6.05 and the viscosity was 7,500 mPa.s (22°C, 1.5 rpm-spindle 63 Brookfield DV II). At this stage 23 g of sodium citrate. $2H_2O$ was added as buffering agent. The pH went up to 7.15 and the viscosity was 40,000 mPa.s (measured as above). The formulation, which appears as a slightly hazy gel, was then packed into a bag-in-can canister equipped with a valve and an applicator and pressurised with nitrogen. If the bag of the bag-in-can system is filled with 104 g of the formulation above then 100 g of the formulation can be delivered through the valve and applicator corresponding to a dose of 1.1 g of xanthan gum.

Example 4 : Treatment of Chronic Pouchitis

The enema of Example 2 was given to twenty adult patients who had previously undergone total colectomy with mucosal proctectomy and ileal J-pouch anal anastomosis for ulcerative colitis and who had active chronic pouchitis refractory to standard therapy. The patients had chronic pouchitis, as defined as continuous symptoms of pouchitis for more than 4 weeks and a Pouchitis Disease Activity Index (PDAI) score of at least 7 points on an 18 point scale. All patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis. Mucosal inflammation, determined by endoscopic examination, was limited to the pouch and did not extend into the ileum proximal to the pouch.

The demographics of the patients entered into the study are presented in Table 1. There were no significant differences in the age, gender distribution, smoking history, time since the diagnosis of ulcerative colitis, duration of pouch function, time since the first episode of pouchitis, duration of the current episode of pouchitis, or in the medications previously used for treatment of pouchitis. All patients had been on medication for

pouchitis, previously, and one half of the patients were on concurrent treatment for chronic pouchitis (Table 2).

Three patients had to discontinue treatment because of worsening of symptoms, but none developed dehydration or required hospitalization. Three patients had cramping discomfort in the pouch after taking the enema. One of the patients who developed cramps discontinued treatment because of the discomfort. One patient developed right lower abdominal pain and the study medication was discontinued.

The initial or final endoscopic or histologic scores of the patients are shown in Table 3.

TABLE 1

PATIENT CHARACTERISTICS

Number of Patients	20
Age (mean)	40(18-62)
Number of Men:Women	12:8
Number of Cigarette Smokers, current:former:never	1:2:17
Years since diagnosis of Ulcerative colitis. Median (range)	9(3-32)
Months of pouch function. Median (range)	45(4-161)
Months since the first episode of pouchitis. Median (range)	42(3-151)
Months of current pouchitis episode. Median (range)	4(0.8-151)

TABLE 2

THERAPY FOR POUCHITIS (20 PATIENTS)

Therapy	No. Of Patients Current	Previous
Antibiotics		
Metronidazole	3	16
Ciprofloxacin	6	15
Amoxicillin/clavulanic acid	1	6
Tetracycline	0	3
Trimethoprine/sulfamethoxazole	1	0
5-ASA		
Sulfasalazine	1	5
Oral mesalamine	0	5
Mesalamine enemas	0	3
Mesalamine suppositories	0	3
Corticoseroids		
Prednisone	1	7
Hydrocortisone enemas	0	5
Immune Modifiers		
Azathioprine	0	0
Cylcosporine	0	0
FK506	0	0
Antidiarrheals		
Loperamide	5	3
Codeine sulfate	0	1

TABLE 3

DISEASE ACTIVITY AT BASELINE AND COMPLETION OF TREATMENT WITH XANTHAN GUM ENEMA

	Baseline Median (range)	Completion Median (range)
Clinical Score	4(1,5)	3(0,4)*
Endoscopy Score	5(1,6)	4(1,6)
Histology Score	2(2,6)	# 2(2,6)
Total Score (PDAI)	11(7,16)	9(2,16)*

*p<0.5 for within-group change. Baseline vs completion (signed rank test with two missing values at completion filled in by overall (groups) Baseline values).

In conclusion, six of the twenty patients discontinued therapy and nine of fourteen patients (64%) who completed the treatment improved (defined as a reduction in the PDAI score of 3 points or more). This is particularly surprising in view of the fact that the patients were refractory to conventional therapy.

CLAIMS

1. A post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition for the treatment or prophylaxis of IBD, said composition comprising a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in an amount effective to treat inflammatory bowel disease, together with a pharmaceutically acceptable carrier or vehicle.

2. A composition as claimed in Claim 1, wherein the polysaccharide is xanthan gum.

3. A composition as claimed in Claim 1, wherein the polysaccharide is HPMC

4. A composition as claimed in any one of the preceding claims, wherein the polysaccharide is present as the sole therapeutically active ingredient.

5. A DRO composition as claimed in any one of the preceding claims.

6. A DRO composition as claimed in Claim 5 which is an enteric coated dosage form adapted to release its contents within the region of the jejunum to the colon.

7. A rectally administrable composition as claimed in any one of Claims 1 to 4.

8. A rectally administrable composition as claimed in Claim 7 which is a liquid enema or foam enema.

9. A liquid enema as claimed in Claim 8, wherein the polysaccharide is xanthan gum in a concentration of 0.4 to 2 % w/w.

10. A foam enema as claimed in Claim 8, wherein the polysaccharide is xanthan gum in a concentration of 1.4 to 2.5 w/w.

11. A liquid enema as claimed in Claim 8, wherein the polysaccharide is HPMC in a concentration of 1 to 20 % w/w.

12. A foam enema as claimed in Claim 8, wherein the polysaccharide is HPMC in a concentration of 2.5 to 25 % w/w.

13. A rectally administrable composition as claimed in Claim 7 or Claim 8, wherein the polysaccharide is xanthan gum in an amount of 400 to 2000 mg per unit dose.

14. A rectally administrable composition as claimed in Claim 7 or Claim 8, wherein the polysaccharide is HPMC in an amount of 1 to 20 g per unit dose.

15. A DRO composition as claimed in Claim 5 or Claim 6, wherein the unit dose of the polysaccharide is 400 to 2000 mg.

16. The use of a polysaccharide selected from xanthan gum and HPMC as a therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

17. A use as claimed in Claim 16, wherein the polysaccharide is the sole therapeutically active agent in the medicament.

18. A use as claimed in Claim 16 or Claim 17 wherein the disease state is pouchitis.

19. A use as claimed in Claim 16 or Claim 17 wherein the disease state is left-sided ulcerative colitis.

20. A use as claimed in Claim 16 or Claim 17 wherein the disease state is Crohn's Disease.

21. A use as claimed in any one of Claims 16 to 20, wherein the medicament is a composition as defined in any one of Claims 1 to 15.

22. A method for the treatment or prophylaxis of IBD comprising contacting the diseased mucosa of the gastro-intestinal tract with a therapeutic amount of a polysaccharide selected from xanthan gum and HPMC.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02899

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/715 A61K9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 04136 A (DAY CHARLES E) 3 March 1994 see page 7, line 21 - line 26	1,2,16, 18-21
X,P	WO 98 01112 A (JENSFELT BIRGITTA ;ASTRA AB (SE)) 15 January 1998 see page 2, line 10 - page 3, line 3 see page 4; example 1	1,3-5,7, 8,11,12, 14-22
X	WO 92 16214 A (NORWICH EATON PHARMA) 1 October 1992 see page 308 see page 33; example 14	1-3,5-8
X	WO 91 01129 A (HENNING BERLIN GMBH) 7 February 1991 see page 8 - page 12; examples 1-3,6	1,3,7,8, 11,12,14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 1999	18/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 03115 A (SLAGEL DAVID ;SACHETTO JEAN PIERRE (CH)) 8 February 1996 see page 12 - page 13; example 1	1,2,4, 7-10,13, 15
X	WO 96 30021 A (MAYO FOUNDATION) 3 October 1996 see page 4 - page 6; examples 1-3	1,2,5-8, 13,15
X	EP 0 517 274 A (CEDONA PHARM BV) 9 December 1992 see page 3; example 1	1,2,7-9, 13
X	FR 2 692 484 A (GOUCHET FRANCK) 24 December 1993 see page 3, line 15 - page 4, line 16 see page 5, line 21 - page 6, line 11	1,3,5,6
X	WO 96 40078 A (CIBUS PHARMACEUTICAL INC) 19 December 1996 see page 42 - page 43; example 4	1,3,5,15
X	CIFTCI K. ET AL: "Delivery of antitumor compounds to the rat colon: in vitro and in vivo evaluation" INT. J. PHARM., vol. 145, no. 1 2, 1996, pages 157-164, XP002092611 see page 158 - page 159	1,3,5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]o \pplication No
PCT/GB 98/02899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9404136 A	03-03-1994	US 5380522 A	10-01-1995
		AU 667955 B	18-04-1996
		AU 4797893 A	15-03-1994
		CA 2142016 A	03-03-1994
		CN 1085084 A	13-04-1994
		EP 0654992 A	31-05-1995
		IL 106640 A	15-04-1997
WO 9801112 A	15-01-1998	AU 3470097 A	02-02-1998
WO 9216214 A	01-10-1992	AU 1577092 A	21-10-1992
		AU 1587392 A	21-10-1992
		WO 9216206 A	01-10-1992
WO 9101129 A	07-02-1991	DE 3924570 A	31-01-1991
		AT 111731 T	15-10-1994
		DE 59007260 D	27-10-1994
		DK 436015 T	12-12-1994
		EP 0436015 A	10-07-1991
		ES 2058932 T	01-11-1994
		JP 4501276 T	05-03-1992
		US 5378470 A	03-01-1995
WO 9603115 A	08-02-1996	AU 2988095 A	22-02-1996
		BR 9508788 A	25-11-1997
		CA 2195079 A	08-02-1996
		CN 1158565 A	03-09-1997
		CZ 9700171 A	16-07-1997
		EP 0774957 A	28-05-1997
		FI 970240 A	20-03-1997
		HU 77528 A	28-05-1998
		NO 970239 A	20-01-1997
		NZ 289903 A	28-10-1998
		PL 318315 A	09-06-1997
		US 5759520 A	02-06-1998
WO 9630021 A	03-10-1996	US 5691343 A	25-11-1997
		AU 5421896 A	16-10-1996
		CA 2216728 A	03-10-1996
		CZ 9703092 A	18-03-1998
		EP 0817634 A	14-01-1998
		HU 9801241 A	28-09-1998
		NO 974440 A	25-09-1997
		NZ 306062 A	28-10-1998
		PL 322526 A	02-02-1998
EP 0517274 A	09-12-1992	DE 4122337 A	14-01-1993
		AT 121934 T	15-05-1995
		AU 1907992 A	08-01-1993
		CA 2110376 A	10-12-1992
		CZ 9302663 A	13-04-1994
		DE 59202096 D	08-06-1995
		DK 586488 T	04-09-1995
		WO 9221324 A	10-12-1992
		EP 0586488 A	16-03-1994
		ES 2074889 T	16-09-1995
		HU 65898 A,B	28-07-1994
		IE 68933 B	24-07-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/02899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0517274 A		RU 2086241 C	10-08-1997
		SK 133793 A	11-05-1994
		US 5352681 A	04-10-1994
		ZA 9204111 A	15-11-1993
FR 2692484 A	24-12-1993	WO 9516451 A	22-06-1995
		AU 5702194 A	03-07-1995
WO 9640078 A	19-12-1996	US 5656294 A	12-08-1997
		US 5811388 A	22-09-1998
		AU 6163096 A	30-12-1996
		CA 2224170 A	19-12-1996
		EP 0831791 A	01-04-1998